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Editorial

Mastering Mechanical Measurements

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I was shocked and saddened to learn of the recent and unexpected passing of Professor Jochen Guck. While I never had the opportunity to meet Jochen in person, only hearing him speak on a couple of occasions at conferences, his work had a profound impact on much of my group's recent research activities. Jochen first came to my attention during his Ph.D. studies. In 2001, while working with Josef Käs at the University of Texas at Austin, he introduced the *optical stretcher*, a dual-beam optical trap able to confine and manipulate cells.[1] While the trapping of microscopic objects using dual-beam optical traps had been described many years previously, most notably by Arthur Ashkin, the use of optical forces to deform or stretch dielectric biological species such as cells had never been properly explored. Since the mechanical properties of a cell are primarily determined by its internal cytoskeleton, a complex network of interlinked microfilaments and microtubules, it was reasonable to assume that variations in mechanical properties might well be correlated with changes in cell status. Accordingly, the ability to accurately measure the deformation of single cells offered a new route to understanding human physiology and disease. The importance of this innovation was immediately obvious to many biologists and clinicians. Put simply, the optical stretcher allowed for contact-free and nondestructive measurement of the mechanical properties of single cells in suspension, solidifying the idea that cellular deformability acts as a sensitive mechanical marker or sensor able to distinguish between cell types and phenotypes. Subsequently, during his time as an independent academic at the University of Leipzig and the Cavendish Laboratory at the University of Cambridge, Jochen began to explore the diagnostic potential of cellular deformability, showing that mechanical phenotyping via optical stretching could be used as label-free method for discriminating and classifying cancer cells.[2]

This endeavor accelerated significantly after Jochen's 2012 move to TU Dresden to take up the Chair of Cellular Machines and his later appointment as a Director at the Max Planck Institute for the Science of Light and the Max Planck Center for Physics and Medicine in Erlangen. Of special note was a growing interest in developing high-throughput mechanical phenotyping tools. While the idea of relating cellular mechanical alterations to human physiology and disease had been embraced by many, the analytical throughputs associated with existing measurement technologies (including the optical stretcher) were unacceptably low, with typical analysis rates of no more than 1 cell per minute. Accordingly, while the mechanical properties of small numbers of single cells could be measured, comprehensive screening of cellular samples containing thousands or millions of cells was simply impossible on realistic time scales, significantly hindering clinical translation. To address this limitation and showcase the potential of deformability as a diagnostic tool, the Guck group introduced real-time deformability cytometry (RT-DC), a technique able to mechanically characterize large populations of cells in short times.[3] In RT-DC, cells are driven through a microfluidic channel constriction and deformed by shear stresses and pressure gradients, rather than optical forces. A sheath flow is used to laterally focus cells within the constriction and inertial lift forces used to center them vertically, thus ensuring that cells are always in focus and never in contact with the channel walls. Deformability can then be simply measured through real-time imaging and image analysis, with throughputs approaching 10,000 cells per minute. In the succeeding years, RT-DC along with the related microfluidic techniques of constriction-based deformability cytometry (cDC),[4] extensional flow deformability cytometry (xDC)[5] and viscoelastic deformability cytometry[6] (vDC, a technique recently developed in my group at ETH Zurich) has cemented high-throughput mechanical phenotyping as a powerful diagnostic tool, allowing biologists to develop a more comprehensive understanding of a range physiological and pathological processes in both biological laboratories and clinical settings. Undeniably, Jochen's early realization that measurement of the (optical) deformability of cells was likely to be a powerful diagnostic of cell status and health laid important foundations for the field of single cell mechanophenotyping and represents a worthy legacy to a visionary scientist.

While this editorial primarily aims to remember and recognize Jochen's contributions to measurement science, it also serves to highlight the importance of leveraging the most appropriate detection modalities when probing biological samples. For example, it is recognized that fluorescence-based methods are the most widely adopted detection modalities in bioanalysis, disease diagnosis, live-cell imaging, and environmental monitoring. The exquisite sensitivity and selectivity of emission spectroscopy is perfectly suited to noninvasively probing the small volumes and low analyte concentrations that are the norm in modern sensing science. That said, fluorescence-based methods often provide limited

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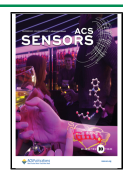

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information (beyond concentration) and commonly require the use of labeling chemistries. Accordingly, expanding the detection toolkit to create a more comprehensive and integrated suite of techniques able to rapidly and noninvasively extract chemical and biological information from complex samples is a priority. In this regard, the use of label-free imaging modalities, such as those used in deformability cytometry, offers an obvious route to increasing information content and quality, with the enumeration of size, shape, morphology and deformation, providing multiple additional dimensions to the detection fingerprint. The rich data sets originating from such integrated approaches when combined with contemporary machine learning models would likely form the basis of a new generation of diagnostic tools that provide high quality information on ultrashort time scales.

Andrew J. deMello, Associate Editor, ACS Sensors orcid.org/0000-0003-1943-1356

AUTHOR INFORMATION

Complete contact information is available at:
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Notes

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